Hermans, L, Van Oosterwijck, J., Goubert, D., Goudman, L., Crombez, C., Calders, P., & Meeus, M. (in press). Inventory of Personal Factors Influencing Conditioned Pain Modulation in Healthy People: A Systematic Literature Review. Pain Practice

Introduction

Pain is a dynamic phenomenon with several excitatory and inhibitory endogenous mechanisms influencing transmission of noxious stimulation[1]. One of the most studied inhibitory mechanisms is Diffuse Noxious Inhibitory Controls (DNIC), also known as the 'pain inhibits pain' phenomenon. Conditioned Pain Modulation (CPM) is the psychophysical procedure to measure this phenomenon. To prevent misinterpretation, only the term CPM will be used continuing the review.

In a prototypical study investigating CPM a conditioning painful stimulation will reduce the intensity of another noxious stimulus. Generally, the noxious stimulation is applied contralateral and outside of the segmental receptive field of the conditioning stimulus[2]. However, different methodological designs are used and there is no golden standard available.

The CPM system is a spinal-medullary-spinal pathway, probably filtering biological relevant signals from the conditioning noxious stimulus, by suppressing the noise induced by a second noxious stimulus [3, 4]. The subnucleus reticularis dorsalis of the caudal medulla, seems to be the key region involved in CPM [4]. In addition, recent findings describe the influence of cortical structures and the limbic system to brain stem structures, which might indicate the involvement of psychological factors in CPM effects [5].

A lot of cross-sectional studies reveal less efficacious CPM in patients with long-term pain[6], meaning that there is no or only limited change in perceived pain intensity for the test stimulus, during application of the conditioning stimulus. The mechanism underlying CPM is hypothesized to be associated with the development of chronic pain[7, 8], since dysfunction of CPM is possibly induced by a shift in balance between pain facilitation and pain inhibition[3]. Furthermore, the prospective study of Yarnitsky et al.[8] shows that less CPM in a pre-operational pain-free state is predictive for the development of chronic pain after surgery. Hence, it seems thus that CPM deficit may constitute a risk factor for the development of chronic pain. Largely unexplored is however the variability in CPM in healthy volunteers, and the individual variables that are associated with this variability. Age and gender are personal factors taken into account regularly, but other possibly influencing individual factors are commonly lacking and may also influence results.

Given the lack of clarity related to the influence of personal factors, like emotional and psychological factors, menstrual cycle, physical activity level, genetics, etc., on CPM, the present study aims at systematically reviewing the scientific literature addressing the influence of personal factors on CPM in healthy people.

Methods

This review is conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines for systematic reviews and meta-analyses of evaluations of health care interventions[9].

Search Strategy

The research question for this systematic review was formulated using the PICO-approach; Does the existing scientific literature provides evidence for personal factors (I) influencing CPM (O) in healthy people (P). The (C) is omitted since the research question concerns healthy people. Based on this PICO question key words and MeSH terms for PIO were used in the electronic databases PubMed and Web of Science to retrieve the existing evidence regarding this topic up to May 2014. Combinations of key words and Mesh terms for CPM were put in the search: diffuse noxious inhibitory control; heterotopic noxious conditioning stimulation; "conditioning pain modulation"; "conditioned pain modulation"; conditioning pain modulation AND pain (MeSH); conditioned pain modulation AND pain (Mesh); counter stimulation AND pain; counter stimulation AND pain (Mesh); counter irritation AND pain; counter irritation AND pain (Mesh); "endogenous modulation"; "endogenous analgesia".

Study selection

Eligibility assessment of the retrieved records was performed by screening against the inclusion and exclusion criteria presented in table 1.

A first screening, was performed based on title and abstract. The article was excluded from the literature review if any of the inclusion criteria were not met. If there was doubt, the full-text article was retrieved and screened. In a 2nd phase all full-texts articles were retrieved and evaluated again to ensure fulfillment of the inclusion criteria. Literature search was performed by two independent researchers (LH and LG) who are both experienced in endogenous pain inhibition research and were

trained in conducting a systematic review by the last author (MM), who is experienced in conducting systematic reviews in this domain.

Risk of Bias

Methodological quality was assessed by two independent researchers (LH and DG), who were blinded for each other's assessment. In case of disagreement a third opinion was provided by the second author (JVO). The first author was trained in assessing methodological quality, the other two researchers (DG and JVO) are experienced in writing systematical reviews. All three researchers are experienced in CPM assessment and pain research. In order to assess the methodological quality of the remaining studies, the "Checklist for RCTs" and the "Checklist for case-control studies", provided by the Dutch Institute for Healthcare Improvement (CBO) and the Dutch Cochrane Centre, were utilized. The case-control and cross sectional studies were coded for 6 items, the RCTs for 11 items (table 2). Each item was answered with either a 'yes', 'no' or 'not applicable' which corresponded to one or zero point. If the article did not provide sufficient information to answer the question, no points were given.

The levels of evidence were assigned to the included articles using the guidelines of the Dutch Institute for Healthcare Improvement (CBO). According to study design and risk of bias, the articles received a level of evidence A1, A2, B, C or D. These levels were used to draw and determine the strength of conclusion. Strength of conclusions was provided independently by two authors (LH and JVO), in case of disagreement there was a third decisive opinion of the last author (MM).

Data Collection Process

An evidence table (Table 3) was established for data extraction. The following items were coded: 1) type of personal factor studied; 2) sample size and characteristics of included participants; 3) procedural characteristics of CPM paradigm procedure; 4) specification of outcome measure for CPM and for the personal factor and 5) results regarding the influence of the personal factor on CPM.

Articles with a methodological quality score less than 50% are included in the evidence table, but excluded from further analysis.

Results

Study Selection

The search strategy resulted in 1536 hits. One potentially relevant article was added by the last author. After removing duplicates 782 studies remained and were screened for eligibility. In the first phase 728 articles were excluded. In the second phase, 8 articles were excluded after reading the full-texts of the remaining 54 articles. In sum, 46 studies were included in this review. Figure 1 shows the selection process for the studies included in this systematic review.

Risk of Bias within Studies

The methodological quality for the included studies are presented in table 2. In 73,8% there was an agreement between the 2 raters (LH and DG). After negotiation full compliance was achieved. Eleven of the included articles evaluated more than one individual factor. Nevertheless, methodological quality was assessed regarding the general topic of the article. Quality assessment revealed 10 studies with a methodological quality less than 50% wherefore they were excluded (21,8%), resulting in a general total methodological quality score of 72,5%. The methodological quality of the RCTs reveal an average score of 68,4%, the case-control studies 76,6% and the cross-sectional studies 64,0%. Overall, most studies lost points because of the lack of blinding and prevention of selection bias.

All the RCTS were downgraded to a level of evidence B, because none of them were double blinded. The case-control studies received all a level of evidence B and the cross-sectional studies displayed a level of evidence C.

Study Characteristics

Twenty-eight of the 46 studies assessed had a case-control design, 14 studies a cross-sectional design and four studies were RCTs. All included articles tested healthy subjects. Only one study compared healthy men, healthy women and women with fibromyalgia[10]. After ruling out the articles with

methodological quality less than 50%, 36 articles remained for further analysis. The sample size of the included studies range from 17 to 191 healthy subjects.

As shown in table 3, a lot of different methodological designs were used evaluating the CPM effect (in six articles different designs within the article): Thermal stimulation (50,0% n=20/40), mechanical pressure (25,0% n=10/40) and electrical stimulation (20,0% n=8/40) were the most frequently used test stimuli. The cold pressor test was the most popular conditioning stimulus, used in 21 out of 39 protocols (53,8%), followed by ischemic (15,4%, n=6/39) and hot water immersion (12,8% or n=5/39). Other infrequent used conditioning stimuli were mechanical stimulation, cold pack, saline injection and heat pain stimulation.

Different outcomes with different units were used to evaluate the magnitude of CPM; nociceptive flexion reflex (NFR) , pressure pain thresholds (PPTs), VAS-scales and other numeric scales to score pain intensity of the test stimulus. The most used outcome measures are pain thresholds and pain intensity ratings.

The characteristics for sample size, intervention, outcome measures and main results are presented in table 3. The evidence table is set up per personal factor, starting with the study with the best methodological quality score.

Evidence regarding the influence of personal factors on CPM in healthy people

<u>Non-modifiable factors</u>

1. *Age*

Six articles examined the effects of age on CPM [7, 11-15]. All studies concluded significant better CPM in younger adults compared to older people or no CPM-effect at all in middle-aged and older persons.

Edwards et al.[7] reported significant CPM effects among younger subjects for the temporal summation (TS) of the last 3-4 heat pulses (out of 10) applied by a thermode during immersion in water of 5°C

(P<.05). Inversely, older participants actually showed increases in thermal pain ratings during cold water immersion (P<0,05) for the first 3-5 heat pulses. This is supported by the study of Riley et al.[13] were the younger group displayed cold water immersion-induced pain inhibition and the older adults experienced enhancement of heat pain. However, Edwards et al.[7] revealed a significant reduction of pulse 5-10 of TS in the older subjects, unlike younger adults, during immersion in non-noxious water of 22°C.

Washington et al.[12] concluded in their study that the magnitude of analgesic response of cold water immersion (2°C) to CO_2-laser and electrical test stimuli was significantly lower in older people (P=0,016). These findings are in accordance with the results of Larivière et al.[11] where younger, middle-aged and older adults were compared. This study detected significant immersion-induced reductions in perceived heat pain intensity in young and middle-aged adults (both P<.05), whereas older adults did not (P=0,09). This is partially in contrast with the recent articles of Riley et al.[14] and Grashorn et al.[15], were no significant difference between middle-aged and older participants was detected. Nevertheless, those two articles also reported significant larger CPM-effects in young compared to middle aged and old.

We can conclude that younger adults have better CPM than older adults and that there is moderate evidence for a possible increase in pain sensitivity during noxious conditioning stimulation in the older adult population (Conclusion strength 2). There is no full consensus for CPM-effect in the middle-aged group, although reduced CPM in this group seems plausible.

2. Gender

Fifteen studies evaluated the influence of gender on CPM[1, 10, 15-27]. In nine studies[1, 15, 17, 19-21, 23, 24, 27] no gender differences were found. Of these nine studies, 5 studies utilized a cold pressor test as conditioning stimulus and the most applied test stimulus was mechanical pressure (n=4/8).

In the study of Rosén et al.[19], electrical and mechanical pain intensity did not differ between males and females during and after heterotopic noxious cold conditioning stimulation. This equal CPM-effect for

both sexes is supported by the study of Oono et al.[24] who used double mechanical stimulation (test stimulus and conditioning stimulus) and did not find a gender-effect. A more recent study of Oono et al.[23] using Quantative Sensory Testing together with mechanical conditioning stimulation revealed again equal CPM responses. Cathcart et al.[20] supported these results by reporting no significant sex differences in CPM evoked by ischemic conditioning stimulation and tested with PPT and TS by manual pressure algometry. Equal CPM responses between genders was also reported by Lautenbacher et al.[17] using hot water as conditioning pain stimulus and computer-controlled algometry for PPT and TS. Baad-Hansen et al.[27] utilized capsaicin-evoked pain to measure the difference in CPM-effect of non-noxious and noxious cold water between men and woman. They also did not find a gender-effect.

In the large sample-sized study of Treister et al.[21] females exhibited same CPM-effects as males regarding noxious cold conditioning stimulation, measured with heat pain intensity. However, using non-noxious cold stimulation, females displayed significantly more CPM compared to males in this study. This is the only study describing a more efficacious CPM in women (p=0,010). In addition, Tousignant-Laflamme et al.[1] and Grashorn et al.[15] found no sex differences in CPM analgesia also using heat pain intensity after respectively during a conditioning cold pressor test.

Six other studies[10, 16, 18, 22, 25, 26] found that men have better CPM than women. The results of Arendt-Nielsen et al.[18] demonstrated that the increases in PPT in males were significantly higher than in females during induced muscle pain (P<0,001) and cold conditioning stimulation (P<0,001). A significant gender-effect was also observed by Granot et al.[25], with a greater endogenous analgesia response in males (P=0,047). In the study of Weissman-Fogel et al.[16] mean CPM extent was a decrease of 1,09 for males and 0,4 for females on a Numeric Pain Scale (P=0,03), however sex difference disappeared after correction for catastrophizing (p=0,09). Ge et al.[26] revealed that PPTs measured from the posterolateral neck muscles following repeated bilateral hypertonic saline injections in the trapezius muscle showed significantly higher PPTs 15 min after the first injection in males than in females (P=0,016). However, PPTs remained at pre-injection level for both sexes when measuring PPTs in the local pain area (M. Trapezius).

Another study[10] examined CPM in healthy males, females and women with fibromyalgia. A reduction of thermal wind-up was solely observed in the healthy male subjects during hot water immersion (P=0,022). A gender effect was also shown by Goodin et al.[22], where men demonstrated a significantly greater magnitude of CPM than women using mechanical pain stimulation and cold water immersion (P<0,05).

Since there are more or less the same number of articles showing a gender-effect versus reporting no significant difference, we conclude that there is no clarity for the influence of sex on CPM.

However, the studies that did find a gender difference, suggest more efficacious CPM-effect in males compared to females since approximately 40% of the articles is showing more CPM in men where there is only one article presenting more CPM in women (Conclusion strength 2).

3. *Menstrual Cycle and Oral Contraceptives*

Six articles investigated the influence of the menstrual cycle or oral contraceptives on CPM[3, 27-32].

Four studies reported no effect of menstrual cycle phase on CPM[3, 28, 31, 32]. In the study of Lindstedt et al.[3] no difference of menstrual cycle phase on the increase of heat pain stimulus, mechanical PPT or NFR threshold, during a submaximal-effort tourniquet test was found. Bartley et al.[31] divided the women in mid-follicular phase and luteal phase and reported equal CPM inhibition on electrocutaneus pain ratings (p=0,272) and NFR magnitudes (p=0,52) during ischemic pain stimulation. In addition, Wilson et al.[32] reported equal CPM in follicular and luteal phase using heat pain stimulation and hot water immersion. These results are supported by Rezaii et al.[28] showing no significant difference in CPM inhibition between low and high estradiol levels, indicating respectively early follicular phase and early luteal phase.

In two other studies[29, 30], women had better pain inhibition during the ovulatory phase. Heat pain intensity varied significantly between phases (P=0,08), with better CPM in women during the ovulatory than during the early follicular phase[29]. Tousignant-Laflamme and Marchand[30] also

found a significant phase effect on CPM (P=0,05) which showed in more detail that the mean reduction in mechanical pain intensity was greater in women during the ovulatory than during the menstrual phase (P=0,02).

Three articles[27, 28, 30] reported the influence of oral contraceptives on CPM. Rezaii et al.[28] described a larger decrease in pressure pain ratings during cold conditioning stimulation in general in women not taking oral contraceptives. However, only for the pressure pain rating at the masseter muscle they found a significant difference. No difference between groups was found in the studies of Baad-Hansen et al.[27] and Tousignant-Laflamme and Marchand[30].

Evidence for the influence of menstrual cycle and oral contraceptives is ambiguous. Nevertheless, CPM seems to be more efficacious in the ovulatory phase compared to the early follicular and luteal phase, with equal CPM in mid-follicular and luteal phase (Conclusion strength 2). The scientific evidence regarding the effect of oral contraceptives on CPM efficacy is conflicting (Conclusion strength 3).

4. Genetics

Two included studies investigated the effect of genetical predisposition on CPM, more specifically serotonin[3, 33] and dopamine-related genes[33]. There was a significant reduced CPM-mediated inhibition for PPTs (p=0,02) and heat-pain (p=0,02), but not for the NFR in the lower serotonin transporter (5-HTT) expressing group[3]. This is partially supported by Treister et al.[33], who found a significant higher magnitude of CPM inhibition in carriers of the long allele of the serotonin transporter gene. However, the latter results were only found using non painful conditioning stimulation. This study did not discover any significant associations between dopamine-related genes and CPM.

There is moderate evidence for larger CPM-effects in people with high 5-HTTT-expressing genotypes (Conclusion strength 3).

5. Ethnicity

Campbell et al.[34] investigated the difference in CPM-effect between non-Hispanic whites and African Americans. Significant larger reductions in electrical pain ratings were found in non-Hispanic whites, although the CPM-effect measured with NFR was comparable. An equal CPM-effect among non-Hispanic black and non-Hispanic white adults was also reported by Riley et al.[14], measuring CPM with heat pain stimulation and cold water immersion. No influence of ethnic background is also confirmed by Goodin et al.[22].

The scientific evidence regarding the influence of ethnic background on CPM is more or less unambiguous and reveals equal responses (Conclusion strength 2).

Modifiable factors

6. Catastrophizing

The effect of catastrophizing on CPM was examined in four studies[16, 22, 25, 35].

One article[16] reported diminished CPM in people with higher catastrophizing levels during a painful stimulus (P=0,02). In addition, Goodin et al.[22] found a positive significant relation between optimism and CPM-effect, whereby optimism was measured prior to the pain assessment. On the contrary, Granot et al.[25] reported an association between greater CPM induced by cold pressor and higher levels of pain catastrophizing measured prior to pain assessment (P=0,028). However, these authors did not observe such correlation when hot water was used as a conditioning stimulus. The influence of naltrexone on CPM in low, moderate and high catastrophizers was investigated by King et al.[35]. They reported a reversed CPM effect in low and moderate catastrophizers, but not in high catastrophizing participants. Nevertheless, in the placebo condition comparable amounts of CPM were shown in the three different groups.

There is conflicting evidence for the effect of catastrophizing on CPM (Conclusion strength 3).

7. Anticipation

To evaluate factors regarding anticipation, possibly influencing CPM, very divers methodological designs were used.

Change in heat pain intensity during conditioning stimulation was positively correlated to the expectations of the participants in the study of Bjørkedal and Flaten[36]. These authors[36] also found that information regarding CPM-effect had corresponding effect in women, though not in men. These influences of expectations and suggestions on CPM-effect are confirmed by the recent NFR-study of Cormier et al.[37], although pain intensity ratings did not differ. Lewis et al.[38] investigated the influence of suggested analgesia on CPM-effect measured by electrical pain intensity and NFR during cold water immersion. There was a significant greater inhibition of the pain intensity, though not for the NFR. Larivière et al.[11] reported a nearly significant ($p=0.057$) positive correlation ($r=0.269$) between expectations and CPM response. However, Grashorn et al.[15] did not find a correlation with expectations in the age-dependent decline of CPM-magnitude.

Two articles[39, 40] explored the effect of attention on CPM, describing a larger CPM-effect when attention is concentrated on the conditioning stimulus compared to the test stimulus. Both studies[39, 40] used pain intensity scales as outcome measure in this procedure. However, when the NFR amplitude was used as outcome measure, Ladouceur et al.[40] could not find a significant alteration of CPM-effect induced by attention.

The influence of distraction on CPM was investigated by two studies. Staud et al.[10] showed equal CPM with and without distraction. This is in contrast with the study of Moont et al.[41] who discovered more analgesia in CPM with distraction compared to CPM alone.

The influence of cognitions was only investigated by studies excluded because of poor methodological quality score.

There is a plausible positive effect of attention to the conditioning stimulus and more CPM measured with pain intensity ratings (Conclusion strength 2). In addition, there is strong evidence for a positive

correlation between expectations and CPM-effect, although no full consensus (Conclusion strength 1). Evidence for the influence of distraction on CPM is conflicting (Conclusion strength 3).

8. *Physical Activity level*

Naugle and Riley[42] was the only article investigating the influence of physical activity on CPM and reported more CPM in greater physically active people.

Higher levels of physical activity seem to correlate with more CPM (Conclusion strength 3).

Discussion

The present study systematically reviewed the scientific literature regarding personal factors influencing CPM in healthy people. The effect of age, gender, menstrual cycle, oral contraceptives, catastrophizing, anticipation, serotonin- and dopamine-related genes, ethnicity and physical activity were described by the included articles. Age, gender, menstrual phase, attention, expectations, physical activity and serotonin-related genes seem to influence the CPM-effect. However, despite the broad search strategy, no studies evaluating the effect of emotional intelligence, body composition, body mass index (BMI) or socioeconomic status were found.

All articles about **age** found better CPM in younger adults compared to older people. Two articles even reported enhanced pain during noxious conditioning stimulation[7,13], and longer aftersensations[13] in the older persons, suggesting impaired CPM in older people. Since neurotransmitters and hormones play an important role in pain modulatory systems, the neuronal and hormonal changes associated with aging are possibly involved in reduced CPM efficacy[43, 44]. Although regarding the latter, Tousignant-Laflamme and Marchand[45] reported equal CPM efficacy in woman with regular menstrual cycles compared to postmenopausal women.

A possible explanation is the age-related decrease in ß-endorphins at rest and a smaller release of ß-endorphins during painful stimulation[13]. The effect of age on Aδ- and C-fibers has already been proven, with predominantly C-fiber input regarding pain in the elderly compared to additional input from Aδ- and C-fibers in younger adults[46]. Consequently, younger people are more prone to a larger CPM-effect when a CPM paradigm is used that activates Aδ-fibers, for example by using a cold pressor test. However, selection bias and the influence of possible confounding factors as attention and task-switching processes probably effect endogenous pain inhibition in the elderly[47]. Furthermore, medication-use and comorbidities are possibly also important factors, and hard to filter out completely. Nevertheless, the included studies tried to exclude participants under medication and with comorbidities describing the participants as ‘healthy for that age’.

Many studies investigated the effect of **gender** on CPM. This literature review revealed moderate evidence for better CPM in males compared to females. One conceivable explanation is the difference in hormones between men and women. Although Baad-Hansen et al.[27] found equal CPM responses in men, women using oral contraceptives and women not using oral contraceptives, the methodologically stronger study of Rezaii et al.[28] revealed a larger CPM-effect in women not taking OC. These latter data are in line with the studies of Kowalczyk et al.[48] and Stening et al.[49] who reported variations in pain responses across the menstrual cycle, depending on fluctuating levels of estradiol and progesterone. According to the findings of this literature review, pain responses across the **menstrual cycle** display more efficacious CPM in the ovulatory phase and less efficacious CPM during the early follicular, mid-follicular and luteal phases. Variations in pain responses because of fluctuating hormone levels could explain gender differences in CPM, showing that women and men only have comparable CPM during the ovulatory phase of women. Fat distribution is different between men and women due to differences in hormonal levels (higher estradiol levels in women). Hence in women, fat is more accumulated around thighs and breasts, while this is more pronounced in the abdomen in men. This can be of influence in CPM assessment depending on the concomitant places of assessment. In addition, women display greater activation of the pregenual medial prefrontal cortex during pain, which implies more self-related attention to pain[50]. Moreover, negative emotional states are more reported in females[25, 51], indicating a possibly anticipational aspect of the gender differences in CPM magnitude.

Gender differences in efficacy of pain inhibition could underlie the increased incidence of some chronic pain conditions predominantly seen in females compared to males.

The influence of **anticipation** was measured with different methodological designs and outcome methods, which makes them hard to combine. Nevertheless, the emotional, attentional and cognitive factors of anticipation are associated with the reticular activating system (RAS), amygdala, cortex and cerebellum. More activation of RAS induces additional consciousness of pain. Subsequently, the different factors of anticipation will accordingly activate or inhibit RAS. In addition, affective states also modulate the amygdala which in turn facilitates or inhibits emotional pain experience[52]. **Attention** to the conditioning stimulus and **positive expectations** seem to have a positive correlation with CPM magnitude[39, 40]. It is largely admitted that paying attention to a nociceptive stimulus induces facilitative pain processing. On the contrary, focusing on another object or task reduces pain[53]. However, in CPM, focus on the conditioning stimulus deadens the pain signals of the test stimulus even more. Directing attention towards the conditioning stimulus may strengthen its subjective intensity and therefore increase its inhibitory effect[39]. Whereas conditioning pain scores were a predictor of CPM effectiveness in men in the study of Treister et al.[21], Granot et al.[25] revealed no such correlation. However, these latter authors[25] additionally suggested that the perception of a painful experience is required to induce effective CPM. In line with this are the individually determined bottom-up capture of attention and the top-down attentional control that go together with other anticipational factors[54].

Although **anxiety** seems to have a significant influence in pain sensation[55], no articles evaluated the influence of anxiety on CPM as main topic. However, three articles[14, 25, 29] with sufficient methodological quality evaluated additionally the correlation/effect of anxiety on CPM by State-Trait Anxiety Inventory or State-Trait Anger Expression Inventory administration. Nevertheless, none of these articles revealed an influence. Seven studies[3, 14, 15, 20, 22, 30, 37] with sufficient methodological quality included a **depression** scale. However, in four studies[3, 20, 30, 37] the influence of depression on CPM was not evaluated, only the comparability of groups regarding depression was examined; if not, depression was introduced as covariate in the analysis. Nonetheless,

Grashorn et al.[15], Riley et al.[14] and Goodin et al.[22] actually explored the influence of depression on CPM, but could not reveal a correlation. In agreement with these results, the case-control study of Normand et al.[56] displayed impaired CPM in patients with fibromyalgia, but efficient CPM in patients with major depressive disorder. However, the patients with major depressive disorder were receiving antidepressive treatment at the moment of testing. Antidepressants block the reuptake of serotonin and norepinephrine transmitters. As a consequence of the important role of serotonin and norepinephrine in pain pathways, this treatment can be an explanation for the normalized CPM observed in these patients.

Subsequently, the hypothetical model of Neugebauer et al.[52] seems a plausible framework: Fear and highly stressful emotions probably activate amygdala-induced inhibitory pathways, albeit depression and anxiety disorders probably initiate amygdala-induced pain-facilitating systems. Consequently, additionally assessed questionnaires, as well as advanced protocols to measure effects of anticipation on CPM are recommended.

Evidence regarding the effect of **information and the influence of distraction** on CPM is limited and conflicting, so more research is required. Also the influence of **catastrophizing** on pain inhibition is contradictory. Goodin et al.[57] found only a significant difference using the in vivo pain catastrophizing scale. This in vivo pain catastrophizing scale, assessed directly after pain assessment, is based on catastrophic thinking during the experimental pain task and probably a better prediction of participants' catastrophizing thoughts for the experimental pain compared to questionnaires prior to assessment, based on general catastrophizing thoughts.

The study of King et al.[35] provides new insights into the role of endogenous opioids on CPM and catastrophizing. After naltrexone induction, reversed CPM-effects were shown in low and moderate catastrophizers, while CPM was unaffected in high catastrophizers. These findings suggest the involvement of multiple systems in CPM. In high catastrophizing people endogenous

pain inhibition might be mediated through other non-opioid mechanisms, for example stress-induced analgesia[35]. In addition, significant correlations of catastrophizing with attention to pain, anticipation of pain, emotional aspects of pain, and motor control have been revealed by fMRI in the study of Gracely et al.[58].

With this search strategy, no studies evaluating **somatization** effects on CPM in healthy people were found. Indeed, somatization is probably of significant influence as the emotions combined will influence pain perception in the above mentioned way. However, somatization in healthy people is sporadic and difficult to measure.

Genetic studies have become essential for unraveling neural mechanisms underlying endogenous pain inhibition. This systematic review included only two studies investigating genetics, more specifically serotonin and dopamine-related genes. Although dopamine seems to play a role in pain modulation with the activity in multiple regions of the pain matrix[59], no associations between dopamine-related genes and CPM were found in the study of Treister et al.[33] The serotonin transporter linked polymorphic region (5-HTTLPR) has a long and a short allele. Both studies in this review showed more CPM inhibition in carriers of the 5-HTTLPR long allele which is coupled with higher 5-HTT receptors. This implies a possible predisposition for people with the 5-HTTLPR short allele to develop chronic pain states like fibromyalgia. An association between fibromyalgia and lower 5-HTT concentrations has already proven by Cohen et al.[60] **Ethnic background** however, appears no predictor of CPM-effect.

Although studies investigating **physical activity** level and CPM in healthy people are sporadic, based on the recent study of Naugle and Riley[42] physical health plays an important role in inducing CPM. Recent research investigating CPM in athletes revealed conflicting results[61, 62]. On one hand, athletes are more capable of handling pain by better coping strategies[61], on the other hand there

is the paradoxical occurrence of athletes developing chronic pain syndromes[62]. So, physical active people show improved CPM, nevertheless a link between (over) trained athletes and chronic pain states exists.

To summarize the main results; this overview shows the personal factors to take in account as possibly influencing CPM: age, gender, menstrual cycle, expectations, attention, physical activity level and serotonin-related genes. Moreover, the 'negative' individual factors (female sex, negative expectations together with anxiety and lower density of the serotonin transporter gene) are frequently present in centrally sensitized patients and contribute to impaired CPM. On the other hand it is possible that impaired CPM in centrally sensitized patients is rather due to the presence of pain and less dependent upon other individual factors. Remains the everlasting question of the chicken and the egg.

It is advised for future research on CPM to take into account 'expectations' (conclusion strength 1), as they seem positively correlated to CPM. Secondly, 'age' is of great importance as younger people show higher CPM (conclusion strength 2). To achieve representative results to the general population, confounding factors related with aging (for example medication use, attention and cognitions) should be taken into account. The third aspect of influence is 'attention'. As attention to the conditioning stimulation seems to evoke more CPM (conclusion strength 2), general standardized instructions concerning the CPM protocol are important. 'Gender' is the fourth factor possibly influencing CPM (conclusion strength 3), so studies separately investigating CPM in women or men are recommended. In addition 'menstrual phase' should be taken into account (conclusion strength 2), since women in this ovulatory phase display higher CPM-effects.

The **strength** of the present review is the broad search strategy. No personal factors were predefined and entered in the search strategy and all studies on CPM in healthy individuals were screened for the role of personal factors.

Unfortunately, comparing and pooling the results was hard because of the heterogeneity of CPM paradigms, outcome measures, design of personal factor, etc.

Further research could be of significant importance to identify the causality of different (combinations of) factors in the risk at chronicity, subsequently prevent chronicity and to select and steer appropriate treatment. Therefore standardized study settings (e.g. same time of immersion and temperature of the water during the cold pressor test and same test stimulus) are warranted and in both healthy controls and patients with central sensitization, taken the above mentioned individual factors into account.

In addition, further research regarding the influence of oral contraceptives, catastrophizing, information about conditioning stimulation, distraction, physical activity and genetics on CPM-magnitude is required since the current literature provides insufficient and conflicting evidence. Thereby, studies concerning emotional intelligence, intelligence quotient, somatization, anxiety, depression, body composition, body mass index and socioeconomic status should be developed.

Conclusion

Based on this systematic review we can conclude that younger age, male sex, the ovulatory phase, positive expectations, attention to the conditioning stimulus, carrying the 5-HTTLPR long allele and level of physical activity are related to a better CPM. Ethnic background seems not of influence. Future studies should examine CPM in healthy people and in patients with central sensitization in the same standardized study setting to obtain firm conclusion and to establish the

role of these factors in the risk for chronicity and to study the modifiable factors as possible points for both preventive and therapeutic approach.

Conflicts of interests

No conflict of interest must be declared.

Table captions

Table 1: Inclusion and exclusion criteria

Table 2: Methodological Quality

Table 3. Evidence table

Figure captions

Figure 1: Flow chart selection process

References

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